Docket No.: 067234-0025 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Fan, Jian-Bing, et al.	Customer No.: 41552
Appl. No.	:	09/779,376	Confirmation No.: 7981
Filed	:	February 07, 2001	
Title	:	NUCLEIC ACID DETECTION METHODS USING UNIVERSAL PRIMING	
Grp./A.U.	:	1634	
Examiner:	:	Lu, Frank Wei Min	

DECLARATION UNDER 37 C.F.R. § 1.132

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Commissioner for Patents
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Alexandria, VA 22313-1450

Sir:

I, Min-Jui Richard Shen, Ph.D., declare as follows:

1) I am a Senior Director of Scientific Research at Illumina, Inc. (Illumina), where I have held this position for two years. Prior to my current position I was Director of Scientific Research between 2003-2005 and prior to that I was Director of Scientific Operations between 2000-2003 at Illumina.

2) Prior to joining Illumina, I was Director of the High-throughput Sequencing Facility between 1999-2000 and Technical Laboratory Manager between 1998-1999 at Myriad Genetics Inc.

3) I obtained a Bachelors of Science majoring in Biochemistry from UCLA in 1986, a Doctorate of Biochemistry from Louisiana State University in 1992. I was a post-doctoral fellow at University of Michigan between 1992-1994 and a post-doctoral fellow at Lawrence Livermore National Laboratory between 1994-1998. I have authored numerous papers in the area of genomics, microarray technology and nucleic acid detection methods. I have pending

and approved patents related to DNA sequencing and genotyping methods. I have been working in the field of DNA analysis for greater than 20 years and have worked in DNA analysis assay development for over 9 years. A copy of my curriculum vitae and a list of publications is attached as Exhibit 1.

4) It has been explained to me that three requirements must be satisfied for a combination of prior art references to render obvious a claimed invention. First, the cited art must teach or suggest all the limitations of the invention as recited in the claims. Second, the cited art, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the ordinary skilled artisan to modify a reference or to combine references. Third, the proposed modification of the cited art must have had a reasonable expectation of success, determined from the vantage point of the ordinary skilled artisan at the time the invention was made. I understand that the following factors are considered in making this determination: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of skill in the pertinent art; and (4) secondary factors of unobviousness.

5) I am vary familiar with the invention claimed in U.S. Patent Application entitled "Nucleic Acid Detection Methods Using Universal Priming" having Serial No. 09/779,376, filed February 7, 2001. I have read the Office Action mailed April 5, 2007, and understand that claims 5, 13, 32, 39, 45 and 57 are rejected under 35 U.S.C. § 103(a) as obvious over Barany et al., U.S. Patent No. 6,534,293 ("Barany et al."), in view of Schneider et al., U.S. Patent No. 4,882,269 ("Schneider et al."). The Examiner concludes that it would have been obvious to one of ordinary skill at the time the invention was made to immobilize a complex described by Barany et al. to a solid support because immobilization would enhance separation of the complex from unhybridized probes and the signal generated from the immobilized complexes with a reasonable expectation of success. I have read both Barany et al. and Schneider et al. and have been asked to render an opinion on whether the claimed invention achieved an unexpected level of detecting nucleotide positions from different samples in the same reaction mixture compared to what one of ordinary skill in the art would have expected at the time the invention was made.

6) For the reasons summarized in this paragraph and detailed in the paragraphs that follow, based on my experience and personal knowledge in the field of nucleotide detection methods, it is my opinion that the person of ordinary skill in the art would not have expected the use of a solid phase immobilization step in combination with ligation complexes as described and claimed in the application to have achieved the claimed results. In particular, the invention claims a method of determining a nucleotide at a detection position in a multiplex format where at least 96 different target sequences are assayed in a common reaction mixture. As the lead developer for Illumina's genotyping assays, achieving accurate and reproducible determination of genotyping targets greater than about 12-24 would have been hailed as a major accomplishment. When we were able to assay 96 different nucleotide determinations ("96plex") in the same reaction mixture, I and others viewed this result as an unprecedented level of advancement in the field. This advancement subsequently opened the door to an entire new era in genomic detection methods that was not previously viewed as possible.

7) The general contention in the Office Action that one would have expected an immobilization step to enhance the signal generated from immobilized complexes because it allows separation of unhybridized probes was not the belief even for those skilled in the field of genotyping. At the time Drs. Fan and Chee made the claimed invention, Illumina had committed substantial effort to research and development for an assay that could accurately and reproducibly determine nucleotide positions in a multiplex format. The goal was to multiplex genotype as many loci as possible in a single reaction. The ability to multiplex 96 different loci simultaneously was a surprise to us and was much greater than what had been achieved prior to the invention.

8) Moreover, the path of experimentation at the time the invention was made generally followed attempts to increase specificity through various modifications within an amplification step or by relying on an enzymatic activity to degrade unhybridized probes in the reaction. Even when compared to such solution phase assays employing additional steps, the use of immobilizing ligation complexes to a solid support provided unexpected levels of multiplexing. To my knowledge, such solution phase assays have even now, more than seven years since the application was filed on the method of the invention, yet to achieve accurate and reproducible results of more than 48 different target sites. In comparison, one competitor

markets a ligation-based multiplex assay employing an enzymatic step to degrade unhybridized ligation probes. This assay is marketed by Applied Biosystems, Inc. ("AB") and is limited to determining only 48 different nucleotide positions in a common reaction mixture. Exhibit 2 is a copy of AB's web site for ordering this assay ("SNPlex™). As shown at the top of Exhibit 2, the SNPlex™ assay "enables the simultaneous genotyping of up to 48 SNPs."

9) At the time the invention was made, I was very familiar with the development efforts with respect to AB's SNPlex™ assay advertised in Exhibit 2. As shown in Exhibit 3, as of 2003, AB was still projecting achieving multiplex levels greater than 48 determinations. However, Exhibit 2, shows that as of present this assay has yet to achieve the goal of more than 48 simultaneous determinations. The fact that AB, who is very experienced in the field has yet to achieve results similar to that which can be achieved by the claimed invention underscores the degree of advancement that was achieved by the invention more than seven years ago.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

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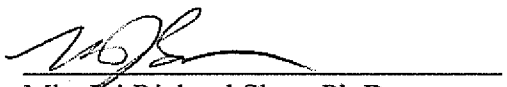
By: 

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Experience:

2007-Current	**Sr. Director of Array Biochemistry**, Illumina, Inc. Assay development and sustaining efforts are the responsibilities of my group. I lead a team of managers that are responsible for the research and development of many high throughput gene expression and genotyping assays.
2005-2007	**Sr. Director of Biochemistry Development**, Illumina, Inc. In this role, I have lead several project teams to develop and expand the Infinium single nucleotide polymorphism genotyping product portfolio. In a matter of 9 months the team launched the HumanHap300 (317k SNP loci on a single chip), HumanHap240S (241k SNP loci), HumanHap550 (555k SNP loci), HumanHap650 (shipping in July), iSelect platform and several custom genotyping products. These products represent the state of the art in genotyping microarray density and quality. I am also the functional manager for the biochemistry development group at Illumina.
2003-2005	**Director of Scientific Research,** Illumina, Inc. As the project manager for the Infinium genotyping product, I lead a multi-disciplinary team of researchers, manufacturing personnel, customer solutions personnel and marketing personnel for the development and launch of the product. The Infinium genotyping product is the next generation highly multiplexed SNP genotyping assay which will enable association studies of complex genetic diseases. I also directed the biochemistry development efforts of the Infinium genotyping assay.
2000-2003	**Director of Scientific Operations,** Illumina, Inc. I managed the day-to-day operations of the High-throughput genotyping facility. The Illumina facility has a capacity of two million genotype calls per day. I also lead reagent manufacturing and assisted them in defining QC methods and metrics. I was on the project team for the BeadLab and BeadStation products from conception to launch. As a project team member, I was responsible for the assay development, reagent manufacturing and integration efforts.
1999-2000	**Director of High-throughput Sequencing Facility**, Myriad Genetics, Inc. I managed the day-to-day operations of the high-throughput sequencing and genotyping facilities. I was directly involved with the assay and process design, and the build out of the high-throughput sequencing facility. I lead the production group that identified and implemented improvements to the production facility. The sequence read pass rate of the facility was greater than 90% with a high of 95%. The facility generated greater than eleven million high quality bases each day.

EXHIBIT 1

1998 - 1999	**Technical Laboratory Manager**, Myriad Genetic Laboratories, Inc. Lead a team that continually refined and improved the quality and efficiency of the DNA sequencing process. We increased the pass rate for the production sequencing facility from a low of 60% (average 75%) to a high of 95% (average 89%). Isolated and removed the common causes of variation within this facility.
1994 - 1998	**Postdoctoral Fellow** with Dr. Harvey Mohrenweiser Lawrence Livermore National Laboratory, Human Genome Center.
1992 - 1994	**Postdoctoral Fellow** with Dr. James R. Baker Jr. University of Michigan Medical Center.
1986 - 1992	**Graduate Research Assistant** with Dr. Prescott L. Deininger (Ph.D. Dissertation Advisor). Louisiana State University Medical Center

Education:

Ph.D.	Biochemistry and Molecular Biology, Louisiana State University Medical Center	1992
B.S.	Biochemistry, UCLA	1986

Managerial Skills

Managerial/Supervisory experience; I managed the quality improvement process in the high-throughput genotyping facility at Illumina and the high-throughput sequencing and genotyping facilities at Myriad Genetics. This encompasses assay development and the coordination and training of the managerial, supervisory and technical staff on how to improve the production facility. My philosophy for quality improvement within any production facility is careful quantification of the production processes to reduce variation and rapid improvements to increase accuracy. The quality improvement process encompasses every aspect of the production process (i.e. assay development, equipment, SOPs, reagent production, software and well trained people).

Team Leader; Illumina develops products under a matrix management approach. A core team of individuals are selected from functional groups (such as manufacturing, research and marketing) to work together for development and launch of the product. I have experience in both roles, as a core team member and core team leader. As a core team member for the BeadLab and BeadStation products I was responsible for assay/process development, reagent manufacturing and integration activities. Currently as a core team leader, I am responsible for the coordination of activities for the development and launch of the Infinium products.

Memberships, Awards and Activities:

2002-present	Member The American Society of Human Genetics.
1986-present	Member American Association for the Advancement of Science.
1995-1996	Laboratory Directed Research and Development grant ($215K) Lawrence Livermore National Laboratory.

1992-1993 Postdoctoral Fellow on the Endocrinology and Metabolism NIH Training Grant. University of Michigan Medical Center.
1987 Cancer Association of Greater New Orleans Research Grant.
1989, 1990 Cancer Association of Greater New Orleans Research Grant.
1991 LSUMC Dean Travel Award for Keystone Symposia.
1988-1989 President, LSUMC Graduate Student Council.
1984-1986 Member of the Board of Directors, Cooperative Housing Association.

Patents filed/granted:

2000 Method for equalizing band intensities on sequencing gels (granted 12/24/2004, USP 6,835,537) Inventors: Nadeem Tusneem, Dimitry Pruss, Min-Jui Richard Shen and Satish K. Bhatnagar.

2002 Multiplex Nucleic Acid Reactions (published 2002) pub. No.: US 2003/0211489 and WO 04/001062, Inventors: Min-Jui Richard Shen, Arnold Oliphant, Scott L. Butler, John R. Stuelpnagel, Mark S. Chee, Kenneth M. Kuhn and Jian-Bing Fan.

2004 Methods and Compositions for Whole Genome Amplification and Genotyping (application submitted, not yet published) Inventors: Min-Jui Richard Shen, Frank Steemers, Weihua Chang and Kevin Gunderson.

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SNPlex™ Genotyping System

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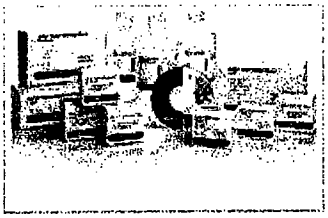

The SNPlex™ Genotyping System enables the simultaneous genotyping of up to 48 SNPs (single nucleotide polymorphisms) against a single biological sample. This system is ideal for fine mapping and candidate gene analysis, population stratification and microarray replication studies.

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SNPlex™ System gDNA Plates Kit	4366135	1 kit
SNPlex™ System Matrix Standard Kit DS-40 (Dye Set S)	4349365	1 kit
SNPlex™ System Array Conditioning Kit	4352018	1 kit
SNPlex™ System Core Kit (Hybridization Plates sold separately)	4362266	1 kit
SNPlex™ System Starter Kit (Core Reagents and Hybridization Plates sold separately)	4362267	1 kit
SNPlex™ System 384 Well Hybridization Plates	4349369	5 plates
SNPlex™ System 96 Well Hybridization Plates	4362933	10 plates
SNPlex™ System Amplification Kit	4349358	1 kit

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The ABI Prism® 3100 and 3100-*Avant* Genetic Analyzers and the Applied Biosystems 3730 and 3730*xl* DNA Analyzers include patented technology licensed from Hitachi, Ltd. as part of a strategic partnership between Applied Biosystems and Hitachi, Ltd., as well as patented technology of Applied Biosystems.

Certain aspects of the technology described herein are covered under current or pending US and/or international patents.

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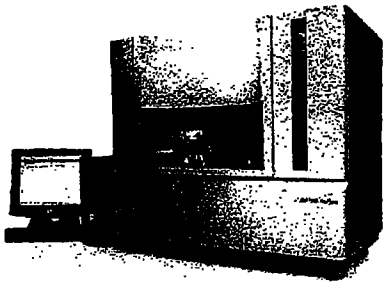
EXHIBIT 3

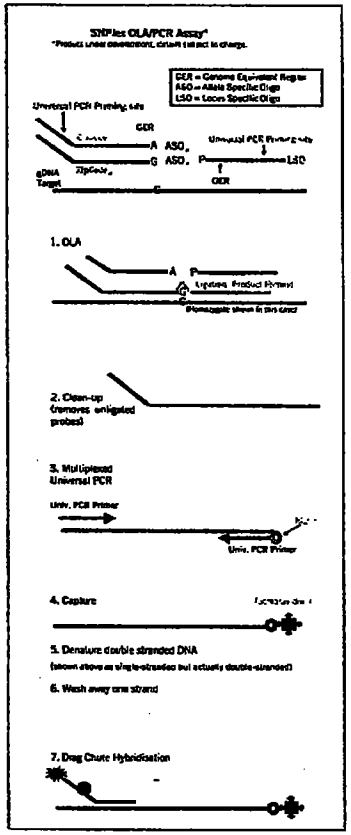
SNPlex™ System Technology

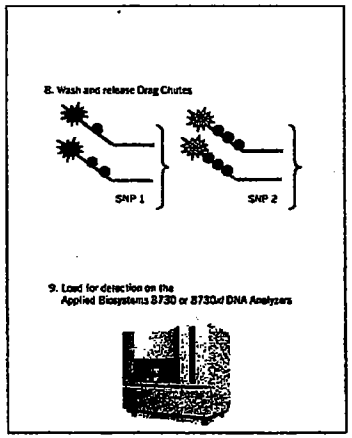
The breakthrough you've been waiting for...

Genomics has quickly emerged as the central basic science of biomedical research with the study of common diseases at the forefront. Initiatives for mapping disease genes requires screening of a large number of individuals, or even entire isolated populations, to further advance our understanding of these complex human diseases. Through the Applera Genome Initiative, Applied Biosystems is enabling this new scale of science. Our commitment to the rapid evolution of innovative tools continues forward with the release of the SNPlex System for Ultra High Throughput SNP Genotyping.

The SNPlex system will bring these ambitious research initiatives within reach. This integrated system delivers cost-efficient, high-throughput genotyping by combining optimised reagent and software components for use on the proven Applied Biosystems 3730 and 3730*xl* capillary electrophoresis-based DNA Analyzers. As the name implies, the SNPlex System allows for 'multiplexed' genotyping of 48-96 SNPs simultaneously in a single biological sample with the ability to detect 4,500 to 9,000 SNPs in parallel in 15 minutes.







The system is based on a proprietary OLA (Oligonucleotide Ligation Assay) technology combined with electrophoretic detection. SNPlex commences with a high specificity, multiplexed OLA to detect target loci in a DNA sample; this is followed by a universal PCR reaction to amplify the resulting ligation products. Detection is carried out using fluorescent labelled, universal reporter probes in conjunction with our high sensitivity electrophoresis solutions and data is analysed using an enhanced auto-allele calling version of the GeneMapper™ Analysis Software.

The continuous assembly, annotation and validation of the human genome sequence content from public sources and from Celera's assembly, along with Applied Biosystems proprietary SNPlex design algorithms allows us to virtually eliminate failures *in silico* and deliver a robust multiplexed assay with a high success rate. SNPlex users will be able to bypass the complex process of design, testing and optimisation of assays and move their research forward faster and more efficiently.

The initial release of the SNPlex system is anticipated in December 2003. Upon release, the product will be available to be purchased in two formats as (a) SNPlex product-based assays designed using customer-provided content and as (b) SNPlex Linkage Mapping Set, a fixed set of ~3,000 markers based on TSC selected SNPs enhanced with Applera content.

Other 'fixed' panels will be announced, and released as multiplexed SNPlex product-based assays, subsequent to the initial product launch.

The combination of custom and fixed SNPlex panels offers maximum versatility for any kind of genetic analysis project, from whole genome linkage analysis to large-scale SNP association studies. SNPlex products will allow laboratories to access state-of-the art technology on the same flexible platform that they already use for sequencing and microsatellite-based genetic mapping applications. No other platform can deliver the versatility, high-throughput, low cost and ease-of-use provided by the Applied Biosystems 3730 and 3730*xl* DNA Analyzers.

Ambitious research projects require the ability to genotype on a grand scale, but until now, technology and cost prevented these projects from advancing. The SNPlex System is the breakthrough we've all been waiting for.

Contact us

Whether you have a question, query or comment on this article, or any of the others in this issue, please get in touch with us at [illegible]

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